Monoclonal Antibodies Specific and Inhibitory to Human Cytochrome P450 2C8, 2C9, 2C18 And 2C19—New Avenues for Drug Discovery

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DHHS Reference No. E–077–99/0 filed 12 Feb 99

Licensing Contract: Dennis Penn; 301/496–7056 ext. 211; e-mail: dp144q@nih.gov

The cytochrome P450 family of enzymes has primary responsibility for the metabolism of xenobiotic drugs and non-drug carcinogens and environmental chemicals, as well as some endobiotics. This laboratory has isolated monoclonal antibodies (MAbs) that are specific to and inhibit the ten major human cytochrome P450s (CYPs) that are responsible for the metabolism of most drugs. The MAb based analytic system identifies the P450s responsible for metabolism of a drug and is thus an entirely new system for Drug Discovery. Drug-drug toxicity can be due to drug partners competing for an individual P450 and be a cause of drug toxicity. Certain drugs given to genetically polymorphic individuals that are defective in a specific P450 can cause serious toxicity to the defective individual. In one case 6–10% of the world population are missing an important P450 (2D6).

The 2C family of cytochrome P450s metabolizes a very large and extensive number of drugs which include tolbutamide, S-Warfarin, mephenytoin, diazepam and taxol. The invention reports the production of inhibitory MAbs to the P450 2C family. The invention describes MAb 5–1–5 and 281–1–1 that specifically inhibit CYP 2C8. MAb 292–2–3 that specifically inhibit CYP 2C9 and MAb 592–2–5 that specifically inhibit both CYP 2C9 and 2C18. MAb 5–7–5 specifically inhibits CYP 2C9, 2C18, and 2C19. In addition MAb 1–68–11 previously reported specifically inhibits all four members of the 2C family, 2C8, 2C9, 2C18, and 2C19. The MAbs may be used as diagnostic probes identifying the single or several P450s responsible for a drugs metabolism and also yield important information on inter-individual differences. The MAb system identifies and characterizes the P450 based metabolism of drugs currently in use and drugs in the screening and development stages of Drug Discovery.

Dated: July 13, 1999.

Jack Spiegel, Ph.D.

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

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BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health.

ACTION: Notice.

SUMMARY: The invention listed below is owned by an agency of the US Government and is available for licensing in the US in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and a copy of the U.S. patent application listed below may be obtained by contacting Susan S. Rucker, J.D., at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7056 ext. 245; fax: 301/402–0220; e-mail:sr156v@nih.gov. A signed Confidential Disclosure Agreement will be required to receive a copy of the patent application.

Immunoadhesins and Methods of Production Thereof

KG Csaky, E Anglade, DM Sullivan (all of NEI), WJ Larochelle (NCI)

Serial No. 08/814,567 filed 10 Mar 97

This patent application relates to the field of immunoadhesins. Immunoadhesins, also known as immunoligands, Ig- or Fc- fusion proteins or chimeras are chimeric molecules comprised of a non-immunoglobulin binding region (e.g., cell surface receptor, ligand, cell adhesion molecule) and an antibody constant domain. Such molecules can be used to identify receptors or ligands, in structure-function studies or as therapeutic agents.

In particular, the application describes a method for producing immunoadhesins which utilizes a replication-deficient adenoviral expression system. This system addresses some of the defects of other immunoadhesion production systems utilizing transfection of plasmid DNA in either a transient or stable system by providing efficient, high level gene expression, appropriate assembly/post-translation modification and ease of purification. Particular immunoadhesins which have been produced using this system are incorporate IL–10, IL–2, IL–13, IL2ra, IL–1ra, mutant IL–4, ICAM, TGF–1β1, or TGF-$\beta1^{223,225}$ as the non-immunoglobulin portion.

This research has been published, in part, in Anglade, et al. ''Interleukin-10 immunoadhesin production by a replication-defective adenovirus'' J. Immunol. Methods 202(1): 41–8 (March 10, 1997).

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Jack Spiegel, Ph.D.,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Cancer Institute Review Group; Subcommittee A—Cancer Centers.

Date: August 5–6, 1999.

Time: 7:00 PM to 1:00 PM.

Agenda: to review and evaluate grant applications.

Place: Embassy Suites, Chevy Chase Pavilion, 4300 Military Rd., Wisconsin at Western Ave., Washington, DC 20015.

Contact: David E. Maslow, PHD, Scientific Review Administrator, Grants Review Branch, Division of Extramural Activities, National Cancer Institute, National Institutes of Health, 6130 Executive Boulevard—EPN